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**ACYLATED BENZYLMAITOSIDES AS INHIBITORS OF SMOOTH
MUSCLE CELL PROLIFERATION**

This application claims the benefit of U.S. Provisional Application No. not yet
5 known, which was converted from U.S. Patent Application No. 09/198,804, filed
November 24, 1998, pursuant to a petition filed under 37 C.F.R. 1.53(c)(2)(i).

BACKGROUND OF THE INVENTION

This invention relates to the use of substituted acylated benzylmalto-
10 smooth muscle cell proliferation inhibitors and as therapeutic compositions for
treating diseases and conditions which are characterized by excessive smooth muscle
proliferation such as restenosis.

All forms of vascular reconstruction such as angioplasty and vein bypass
15 procedures effect a response to injury that ultimately leads to smooth muscle cell
(SMC) proliferation and subsequently, deposition of profuse amounts of
extracellular matrix (Clowes, A. W.; Reidy, M. A. *J. Vasc. Surg* **1991**, 13, 885).
These events are also central processes in the pathogenesis of atherosclerosis (Raines
E.W.; Ross R. *Br. Heart J.* **1993**, 69 (Supplement), S. 30) as well as transplant
20 arteriosclerosis (Isik, F.F.; McDonald, T. O.; Ferguson, M.; Yamanaka, E.; Gordon
Am. J. Pathol. **1992**, 141, 1139). In the case of restenosis following angioplasty,
clinically relevant solutions for controlling SMC proliferation through
pharmacological intervention have remained elusive to date (Herrman, J. P. R.;
Hermans, W.R.M.; Vos, J.; Serruys P. W. *Drugs* **1993**, 4, 18 and 249). Any
25 successful approach to selective SMC proliferation inhibition must not interfere with
endothelial cell repair or the normal proliferation and function of other cells
(Weissberg, P.L.; Grainger, D.J.; Shanahan C.M.; Metcalfe, J.C. *Cardiovascular
Res.* **1993**, 27, 1191).

The glycosaminoglycans heparin and heparan sulfate are endogenous
30 inhibitors of SMC proliferation, yet are able to promote endothelial cell growth
(Castellot, J.J. Jr.; Wright, T. C.; Karnovsky, M.J. *Seminars in Thrombosis and
Hemostasis* **1987**, 13, 489). However, the full clinical benefits of heparin, heparin
fragments, chemically modified heparin, low molecular weight heparins, and other

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heparin mimicking anionic polysaccharides may be compromised due to other pharmacological liabilities (excessive bleeding arising from anticoagulation effects, in particular) coupled with heterogeneity of the various preparations (Borman, S. *Chemical and Engineering News*, 1993, June 28, 27).

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WO 96/14325 discloses acylated benzylglycosides as smooth muscle cell proliferation inhibitors. The compounds of the present invention differ in that the substituents on the carbohydrate backbone are different.

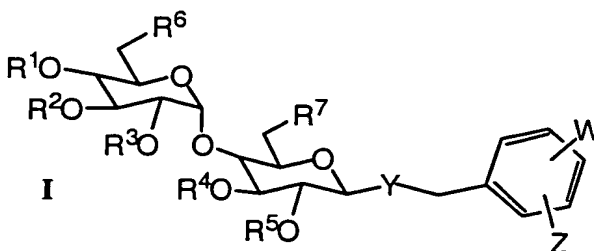
10 Zehavi, U.; Herchman, M. in *Carbohydr. Res.* 1986, 151, 371, disclosed 4-carboxy-2-nitrobenzyl 4-O- α -D-glucopyranosyl- β -D-glucopyranoside which is attached to a polymer for study as an acceptor in the glycogen synthase reaction. The compounds of the present invention differ in that the substituents on the benzyl groups are different and the use (smooth muscle antiproliferation) is different.

15 Patent numbers US 5,498,775, WO96/14324, and US 5,464,827 describe polyanionic benzylglycosides or cyclodextrins as smooth muscle cell proliferation inhibitors for treating diseases and conditions which are characterized by excessive smooth muscle proliferation. β -cyclodextrin tetradecasulfate has been described as a smooth muscle cell proliferation inhibitor and as an effective inhibitor of restenosis (Reilly, C.F.; Fujita, T.; McFall, R. C.; Stabilito, I. I.; Wai-se E.; Johnson, R. G. 20 *Drug Development Research* 1993, 29, 137). US 5019562 discloses anionic derivatives of cyclodextrins for treating pathological conditions associated with undesirable cell or tissue growth. WO 93/09790 discloses antiproliferative polyanionic derivatives of cyclodextrins bearing at least 2 anionic residues per carbohydrate residues. Meinetsberger (EP 312087 A2 and EP 312086 A2) describes 25 the antithrombotic and anticoagulant properties of sulfated bis-aldonic acid amides. US 4431637 discloses polysulfated phenolic glycosides as modulators of the complement system. The compounds of the present invention differ from all of the prior art in that the compounds (a) are benzylmaltosides which bear no structural resemblance to heparin, sulfated cyclodextrins, or to sulfated lactobionic acid dimers, 30 (b) contain no more than two contiguous sugar residues (disaccharide), (c) are of a defined structure, (d) and are not sulfated.

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DESCRIPTION OF THE INVENTION

This invention provides benzylmaltosides of formula I



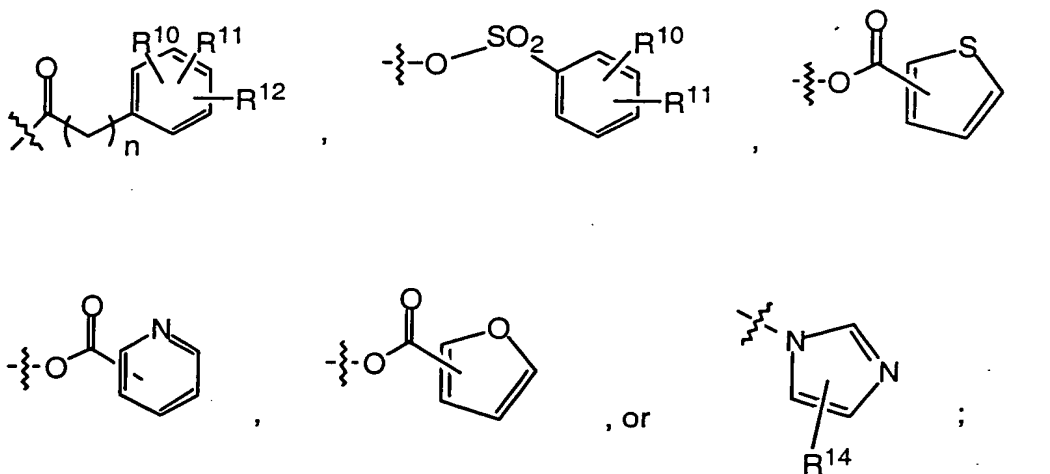
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wherein

R¹, R², R³, R⁴, and R⁵ are each, independently, hydrogen, acyl of 2-7 carbon atoms, haloacyl of 2-7 carbon atoms, nitroacyl of 2-7 carbon atoms, cyanoacyl of 2-7 carbon atoms, trifluoromethylacyl of 3-8 carbon atoms, or benzoyl in which the phenyl moiety is substituted with R⁸;

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R⁶ and R⁷ are each, independently, -OH, -OR⁹, O-tert-butyldimethylsilyl, O-trialkylsilyl of 1-6 carbon atoms per alkyl moiety, O-triphenylsilyl,



15

R⁸, R¹⁰, R¹¹, and R¹² are each, independently, hydrogen, -CN, -NO₂, halogen, CF₃, alkyl of 1-6 carbon atoms, acetyl, benzoyl, or alkoxy of 1-6 carbon atoms;

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R⁹ is acyl of 2-7 carbon atoms, haloacyl of 2-7 carbon atoms, nitroacyl of 2-7 carbon atoms, cyanoacyl of 2-7 carbon atoms, trifluoromethylacyl of 3-8 carbon atoms, or benzoyl in which the phenyl moiety is substituted with R⁸;

Y is O, S, NH, NMe, or CH₂;

- 5 W is halogen, -CN, CF₃, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, nitroalkyl of 1-6 carbon atoms, cyanoalkyl of 1-6 carbon atoms, alkoxyalkyl of 2-12 carbon atoms, alkoxy of 1-6 carbon atoms, or phenyl mono-, di-, or tri-substituted with R⁸;

Z is -NO₂, -NH₂, -NHR¹³, or -NHCO-Het;

- 10 R¹³ is acyl of 2-7 carbon atoms, haloacyl of 2-7 carbon atoms, nitroacyl of 2-7 carbon atoms, cyanoacyl of 2-7 carbon atoms, trifluoromethylacyl of 3-8 carbon atoms, benzoyl in which the phenyl moiety is substituted with R⁸, or

- R¹³ is an α -amino acid in which the α carboxyl group forms an amide with the nitrogen of Z, wherein if said amino acid is glutamic acid or aspartic acid, the
15 non- α carboxylic acid is an alkyl ester in which the alkyl moiety contains from 1-6 carbon atoms;

Het is pyridyl substituted with R⁸, thienyl substituted with R⁸, furyl substituted with R⁸, oxazolyl substituted with R⁸, pyrazinyl substituted with R⁸, pyrimidinyl substituted with R⁸, or thiazolyl substituted with R⁸;

- 20 R¹⁴ is R⁸, -NH₂, -CO₂H, or -NH-acyl of 2-7 carbon atoms;

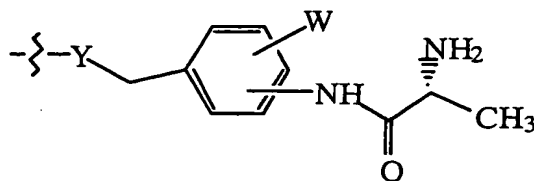
n = 0-3;

with the proviso that when Z is -NHR¹³ and Y is O, at least one of R¹, R², R³, R⁴, and R⁵ is hydrogen, or at least one of R⁶ and R⁷ is OH, or a pharmaceutically acceptable salt thereof.

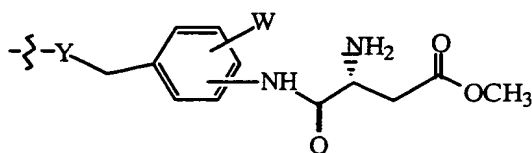
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Alkyl includes both straight chain as well as branched moieties. Halogen means bromine, chlorine, fluorine, and iodine. When R¹³ is an α -amino acid, the carboxyl moiety exists as an amide with the amide nitrogen being bonded to the phenyl ring of the compound of formula I. The following exemplifies the resulting
30 structure when R¹³ is alanine:

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When the amino acid contains a second carboxyl moiety, the moiety is an
5 alkyl ester of the free acid. The following example shows aspartic acid methyl ester.



Preferred amino acids include alanine, arginine, aspartic acid, cystine,
10 glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. The amino acids defined by R^{13} include both the D and L amino acids.

Pharmaceutically acceptable salts can be formed from organic and inorganic
15 acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids. Salts may also be formed from organic and inorganic bases, preferably alkali metal salts, for example, sodium,
20 lithium, or potassium. Acid addition salts can be prepared when Y contains a nitrogen or the compound of formula I contains a basic nitrogen, and base addition salts can typically be prepared when the compound of formula I contains a hydroxyl group.

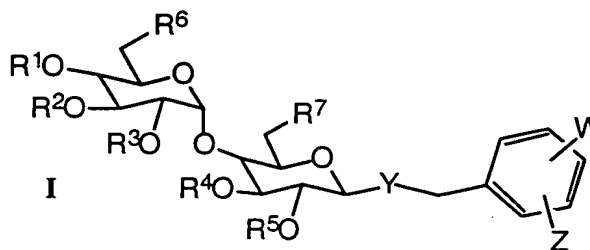
25 The compounds of this invention may contain an asymmetric carbon atom or sulfoxide moiety and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers.

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While shown without respect to stereochemistry in Formula I, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

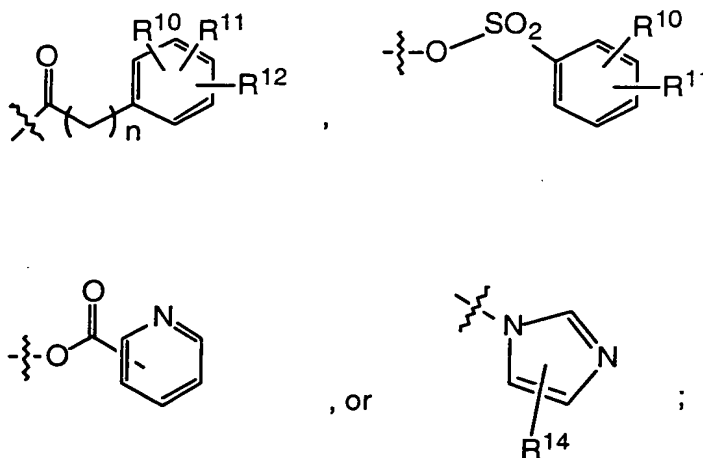
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Preferred compounds of this invention are benzylmaltosides of formula I



10 wherein

R^1 , R^2 , R^3 , R^4 , and R^5 are each, independently, hydrogen or acyl of 2-7 carbon;
 R^6 and R^7 are each, independently, -OH, -OR⁹, O-tert-butyl dimethylsilyl,



15

R^8 , R^{10} , R^{11} , and R^{12} are each, independently, hydrogen, -CN, -NO₂, halogen, CF₃, alkyl of 1-6 carbon atoms, acetyl, benzoyl, or alkoxy of 1-6 carbon atoms;
 R^9 is acyl of 2-7 carbon atoms, or benzoyl in which the phenyl moiety is substituted with R^8 ;

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Y is O or S;

W is halogen, or alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, nitroalkyl of 1-6 carbon atoms, cyanoalkyl of 1-6 carbon atoms, alkoxyalkyl of 2-12 carbon atoms, alkoxy of 1-6 carbon atoms, or phenyl mono-, di-, or tri-substituted with R⁸;

Z is -NO₂, -NH₂, -NHR¹³, or -NHCO-Het;

R¹³ is acyl of 2-7 carbon atoms, or benzoyl in which the phenyl moiety is substituted with R⁸, or

R¹³ is an α -amino acid in which the α carboxyl group forms an amide with the nitrogen of Z, wherein if said amino acid is glutamic acid or aspartic acid, the non- α carboxylic acid is an alkyl ester in which the alkyl moiety contains from 1-6 carbon atoms;

Het is pyridyl substituted with R⁸, thienyl substituted with R⁸, furyl substituted with R⁸, oxazolyl substituted with R⁸, pyrazinyl substituted with R⁸, pyrimidinyl substituted with R⁸, or thiazolyl substituted with R⁸;

R¹⁴ is R⁸, -NH₂, -CO₂H, or -NH-acyl of 2-7 carbon atoms;

n = 0-3;

with the proviso that when Z is -NHR¹³ and Y is O, at least one of R¹, R², R³, R⁴, and R⁵ is hydrogen, or at least one of R⁶ and R⁷ is OH, or a pharmaceutically acceptable salt thereof.

Specifically preferred compounds of this invention are:

4-Chloro-3-nitro-benzyl- β -D-maltoside heptaacetate or a pharmaceutically acceptable salt thereof;

N-{5-[(Hepta-*O*-acetyl- β -D-maltosyloxy)-methyl]-2-chloro-phenyl}-L-aspartamide- γ -*tert*-butyl ester or a pharmaceutically acceptable salt thereof;

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- N*-{2-Chloro-5-[(2,2',3,3',4',6,6')-hepta-*O*-acetyl- β -D-maltosyl-oxymethyl]-phenyl}-
(9*H*-fluoren-9-ylmethoxycarbonyl)-L-alaninamide or a pharmaceutically acceptable
salt thereof;
- 5 4-Benzoyl-*N*-{2-chloro-5-[(2,2',3,3',4',6,6')-hepta-*O*-acetyl- β -D-maltosyl)-oxy-
methyl]- phenyl}-benzamide or a pharmaceutically acceptable salt thereof;
- (4-Chloro-3-nitro-benzyl) -hepta-*O*-acetyl-1-thio- β -D-maltoside or a pharmaceutically
acceptable salt thereof;
- 10 (3-Amino-4-chloro-benzyl) hepta-*O*-acetyl-1-thio- β -D-maltoside or a
pharmaceutically acceptable salt thereof;
- N*-{2-chloro-5-[hepta-*O*-acetyl- β -D-maltosyl-1-thio)-methyl]-phenyl}-acetamide or a
15 pharmaceutically acceptable salt thereof;
- 5-[(Hepta-*O*-acetyl- β -D-maltosyl)-oxy-methyl]-2-cyano-1-nitrobenzene or a
pharmaceutically acceptable salt thereof.
- 20 *N*-[2-Chloro-5-(β -D-maltosyl-oxymethyl)-phenyl]-acetamide or a pharmaceutically
acceptable salt thereof;
- N*-{5-[6,6'-Di-*O*-(*tert*-butyl-dimethyl-silyl)- β -D-maltosyloxy-methyl]-2-methyl-
phenyl}- acetamide or a pharmaceutically acceptable salt thereof;
- 25 *N*-{2-Chloro-5-[6,6'-di-*O*-(*tert*-butyl-dimethyl-silyl)- β -D-maltosyloxy-methyl]-
phenyl}- acetamide or a pharmaceutically acceptable salt thereof;
- N*-{2-Chloro-5-[[6,6'-di-*O*-benzoyl- β -D-maltosyl]oxy)methyl]phenyl}-acetamide or
30 a pharmaceutically acceptable salt thereof;

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N-{2-Chloro-5-[[([6,6'-di-*O*-benzoyl-2,2',3,3',4'-penta-acetyl- β -D-maltosyl]oxy)-methyl]phenyl}-acetamide or a pharmaceutically acceptable salt thereof;

(4-Chloro-3-nitrophenyl)methyl-4-*O*-[6-*O*-(3-pyridinylcarbonyl)- α -D-glucopyranosyl]- β -D-glucopyranoside-6-(3-pyridinecarboxylate) or a pharmaceutically acceptable salt thereof;

(4-Chloro-3-nitrophenyl)methyl-4-*O*-[6-*O*-(3-pyridinylcarbonyl)- α -D-glucopyranosyl]- β -D-glucopyranoside or a pharmaceutically acceptable salt thereof;

10

N-[2-Chloro-5-[[4-*O*- α -D-glucopyranosyl- β -D-glucopyranosyl]oxy]methyl]phenyl]-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof;

Benzoic acid 6-{4-chloro-3-[(pyridine-3-carbonyl)-amino]-benzyloxy}-4,5-dihydroxy-3-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-tetrahydro-pyran-2-ylmethyl ester or a pharmaceutically acceptable salt thereof;

(4-Chloro-3-nitro-benzyl)-1-deoxy-1-thio- β -D-maltoside or a pharmaceutically acceptable salt thereof;

20

N-{2-chloro-5-[β -D-maltosyl-1-thio]-methyl]-phenyl}-acetamide or a pharmaceutically acceptable salt thereof;

5-[[6,6'-Bis-*O*-(4-toluenesulfonyl)- β -maltosyl]-oxy-methyl]-2-methyl-1-nitrobenzene or a pharmaceutically acceptable salt thereof;

25

5-[[2,2',3,3',4'-Penta-*O*-acetyl-6,6'-bis-*O*-(4-toluenesulfonyl)- β -maltosyl]-oxy-methyl]-2-methyl-1-nitrobenzene or a pharmaceutically acceptable salt thereof;

30

5-[[6,6'-Dideoxy-6,6'-bis(4-nitro-imidazol-1-yl)- β -maltosyl]-oxy-methyl]-2-methyl-1-nitrobenzene or a pharmaceutically acceptable salt thereof; and

- 10 -

5-{{[2,2',3,3',4'-Penta-*O*-acetyl-6,6'-dideoxy-6,6'-bis(4-nitro-imidazol-1-yl)- β -maltosyl]-oxy-methyl}-2-methyl-1-nitrobenzene or a pharmaceutically acceptable salt thereof.

5

The compounds of this invention were be prepared according to the following schemes from commercially available starting materials or starting materials which can be prepared using literature procedures. These schemes show the preparation of representative compounds of this invention.

Acetobromomaltose **1** is coupled with a benzyl alcohol **2** in the presence of a catalyst such as a mercuric bromide, mercuric cyanide, silver triflate, or silver perchlorate in an aprotic solvent such as acetonitrile, dichloromethane, ether, toluene or nitromethane at temperatures ranging from -40 °C to reflux to yield glycoside **3** (Scheme 1). This glycosidation can also be accomplished using Schmidt's trichloroacetimidate coupling with zinc bromide in a solvent such as dichloromethane. Reduction of the nitro group of **3** can be accomplished with a reducing agent such as stannous chloride in a polar aprotic solvent such as ethyl acetate at ambient temperature to reflux to afford an anilino compound **4**. Coupling of **4** with an acid chloride can be completed in the presence of an amine base such as triethylamine or diisopropylethylamine or using a stronger base such as sodium hydride (for sterically hindered systems) in an aprotic solvent such as dichloromethane or tetrahydrofuran at temperatures ranging from 0 °C to ambient temperature to yield the target compound **5**. The peracetylated compound **5** can be converted to the heptahydroxy compound **6** with catalytic sodium methoxide in methanol or aqueous sodium hydroxide in methanol at temperatures ranging from ambient temperature to reflux.

As illustrated in Scheme 2, the C-6 and C-6' positions can be selectively protected as a silyl ether (**7**) using *t*-butyldimethylchlorosilane, a tertiary base such as triethylamine, and a catalytic amount of 4-dimethylaminopyridine. In addition, the 6- and 6'-position primary alcohols can be selectively acylated (Scheme 3) using an

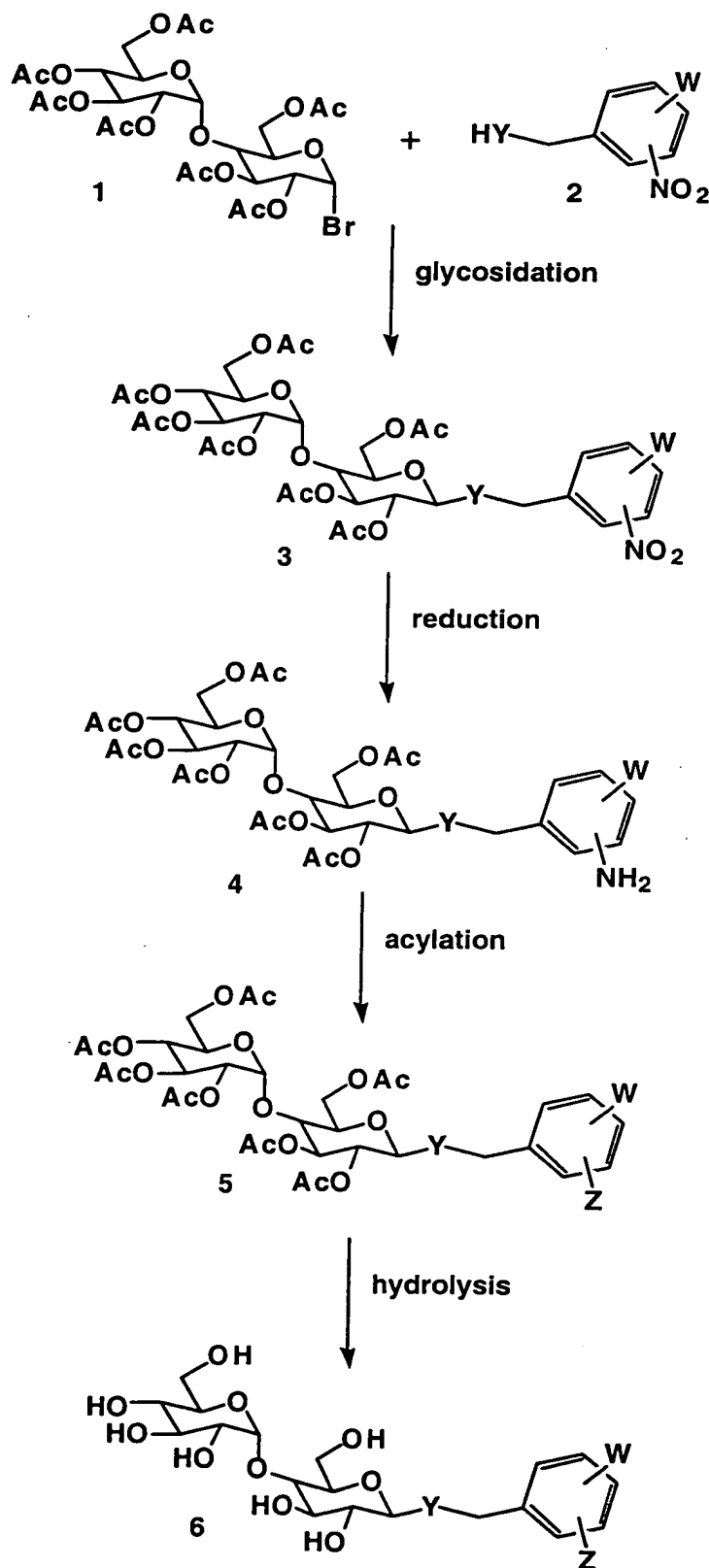
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appropriate acid chloride in a 1:1 mixture of tetrahydrofuran and the hindered base 2,4,6-collidine at -40 °C initially to ambient temperature overnight. The remaining five secondary alcohols of the disaccharide can then be protected with acetic anhydride and triethylamine in a solvent such as dichloromethane to afford the
5 peracetylated compound 8.

In **Scheme 4** the two primary alcohol positions (*C*-6 and *C*-6') are first converted to tosylates using tosyl chloride and pyridine in a solvent such as dichloromethane; the resulting intermediate is then peracetylated as mentioned above to generate compound 9. Through displacement of the tosylates of 9, heterocyclic
10 ring systems can be incorporated at the 6 and 6' positions. Finally, the five secondary acetates are removed with catalytic sodium methoxide in methanol or aqueous sodium hydroxide in methanol at temperatures ranging from ambient temperature to reflux to afford compound 10.

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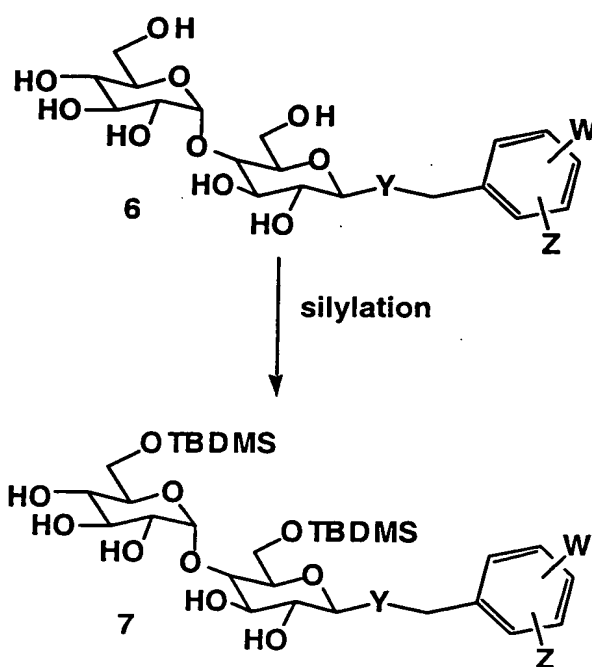
Schem 1



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If $R_2 = \text{OH}$ or OTBDMS:

Scheme 2

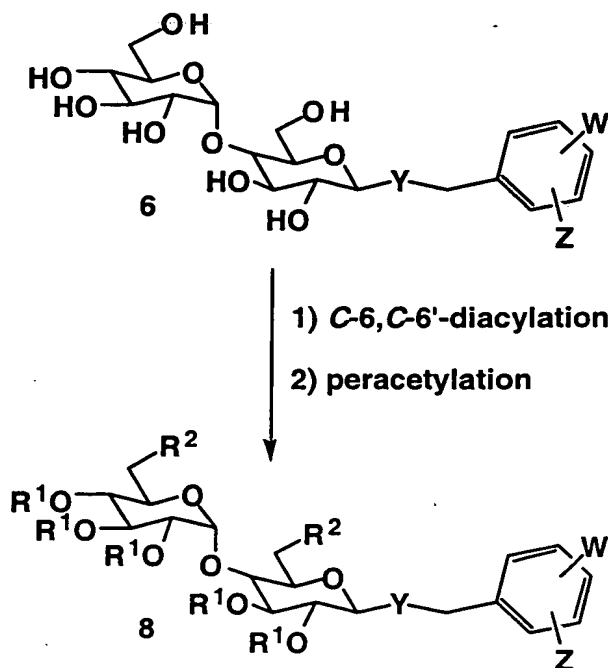


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If $R_2 = \text{ester linkage}$:

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Scheme 3

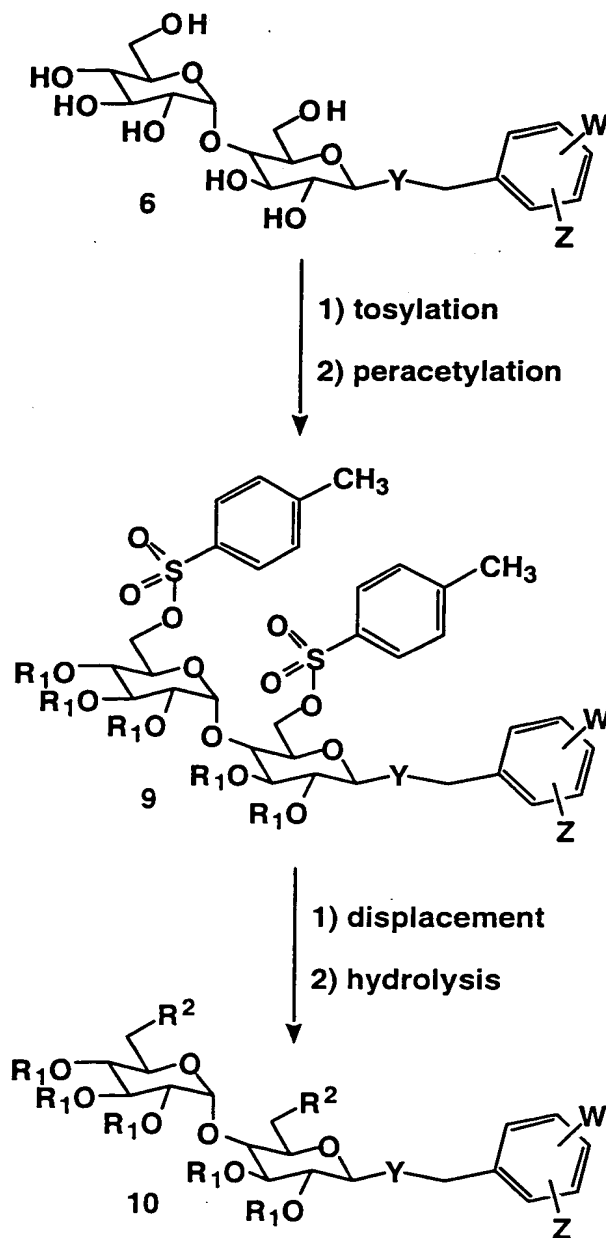


If R_2 = tosylate or imidazole:

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Scheme 4



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The compounds of this invention are useful as antiproliferative agents. The following procedures show the evaluation of representative compounds of this invention in standard pharmacological test procedure which measured ability of the evaluated compound to inhibit smooth muscle cell proliferation

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Effects of Compounds on Cell Proliferation Using ^3H Thymidine Incorporation

Human and porcine smooth muscle cells were tested in early passage (generally passage 3 - 7) at sub-confluent conditions. Cultures were grown in 16 mm (24 well) multi-well culture dishes in medium 199 supplemented with 10% fetal bovine serum and 2% antibiotic / antimycotic. At sub-confluence, the cells were placed in a defined serum free medium (AIM-V; Gibco) for 24 - 48 h prior to initiating the experimental protocol.

Although compounds were found to be more effective with longer pre-incubations, in general, the procedures were initiated with the addition of compound, ^3H thymidine and serum / growth factor to serum deprived synchronized cells and results are reported accordingly.

Compounds were added to each well at 50 fold dilution (20 μL / well) and the plates were incubated for 24 - 36 h at 37 $^{\circ}\text{C}$ in 5% CO_2 . Compounds were initially dissolved in 50% ethanol and serially diluted into media. Compounds were routinely evaluated at concentrations from 1 to 100 μM . As a control, grade II porcine intestinal mucosal heparin (sodium salt) was routinely evaluated in all cell preparations at concentrations from 0.1 to 100 $\mu\text{g/mL}$.

At the completion of the test procedure, plates were placed on ice, washed three times with ice cold phosphate buffered saline (PBS) and incubated in ice cold 10% trichloroacetic acid (TCA) for 30 min to remove acid soluble proteins. Solution was transferred to scintillation vials containing 0.4 N HCl (500 μL / vial to neutralize NaOH) and each well was rinsed two times with water (500 μL) for a total volume of 2 mL / vial.

Data was obtained, in triplicate, for both control and experimental samples. Control (100%) data was obtained from maximally stimulated cells, as the result of growth factor or serum stimulation. Experimental data was obtained from cells maximally stimulated with growth factor or serum and treated with compound. Data are expressed as an IC_{50} or percent inhibition in Table I below.

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Table 1.

Compound of Example	Porcine Smooth Muscle Cell Antiproliferation IC50
1	0.850 μ M
2	4.61 μ M
3	1.71 μ M
4	0.164 μ M
5	1.14 μ M
6	0.667 μ M
7	7.97 μ M
8	2.05 μ M
9	0% @ 500 μ M
10	6.10 μ M
11	3.90 μ M
12	0.390-2.20 μ M
13	0.360 μ M
14	6.56 μ M
15	73.2 μ M
16	18% @ 50 μ M
17	0.245 μ M
18	25% @ 50 μ M
19	28% @ 50 μ M
20	0.740 μ M
21	67.4 μ M
22	23% @ 100 μ M
23	4.70 μ M

The compounds of this invention are useful in treating or inhibiting diseases which are characterized by excessive smooth muscle cell proliferation (smooth muscle cell hyperproliferation). The compounds are particularly useful in treating hyperproliferative vascular diseases which are characterized by smooth muscle cell hyperproliferation, such as restenosis, which most frequently arises from vascular reconstructive surgery and transplantation, for example, balloon angioplasty, vascular graft surgery, coronary artery bypass surgery, and heart transplantation. Other disease states in which there is unwanted "cellular" vascular proliferation include hypertension, asthma, and congestive heart failure. The compounds of this invention are also useful as inhibitors of angiogenesis. Angiogenesis (neovascularization), the process by which new capillaries are formed, is of principal importance for a number

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of pathological events including chronic inflammation and malignant processes. The compounds of this invention are therefore useful as antineoplastic agents.

5 The compounds of this invention can be formulated neat or with a pharmaceutical carrier for administration, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmacological practice. The pharmaceutical carrier may be solid or liquid.

10 A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is
15 mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose,
20 polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid
25 carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably
30 sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, lethicins, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration.

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The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds of this invention can also be administered orally either in liquid or solid composition form.

The compounds of this invention may be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Based on the results obtained in the standard pharmacological test procedures, projected daily dosages of active compound would be 0.1 to 10 mg/kg administered parenterally (intravenous preferred), with projected daily oral dosage being approximately ten-fold higher. Anticipated intravenous administration would last for approximately 5-30 days following acute vascular injury (i.e., balloon angioplasty or transplantation) and for a longer duration for the treatment of chronic disorders. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the

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administering physician based on experience with the individual subject treated. Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged
5 compositions, for example, packaged powders, vials, ampoules, pre filled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

10 The following provides the preparation of representative compounds of this invention.

Example 1

15 4-Chloro-3-nitro-benzyl- β -D-maltoside heptaacetate

To a stirred solution of 4-chloro-3-nitrobenzyl alcohol (6.70 g, 35.7 mmol) and HgBr_2 (14.2 g, 39.3 mmol) in freshly distilled CH_3CN (239 mL) was added in one portion $\text{Hg}(\text{CN})_2$ (9.02 g, 35.7 mmol). After 0.5 h, acetobromomaltose (25.0 g, 35.7 mmol) was added, and the mixture stirred for 18 h at rt. The reaction was then
20 quenched with a mixture of H_2O :brine (1:1, 100 mL) and extracted with 10% CH_2Cl_2 :EtOAc. The combined organic extracts were dried (MgSO_4) and concentrated. Purification by flash chromatography (10:90 to 80:20 EtOAc:petroleum ether gradient) gave 51.9 g (90%) of the title compound as a glassy oil which was recrystallized from Et_2O :petroleum ether to afford a glassy white solid, mp 107-111
25 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 2.00 (s, 3H), 2.02 (s, 3H), 2.03, (s, 3H), 2.04 (s, 6H), 2.11 (s, 3H), 2.15 (s, 3H), 3.70 (ddd, $J = 2.9, 4.2, 9.7$ Hz, 1H), 3.94-3.98 (m, 1H), 4.01-4.07 (m, 2H), 4.20-4.28 (m, 2H), 4.54 (dd, $J = 2.9, 12.3$ Hz, 1H), 4.63-4.68 (m, 2H), 4.84-4.94 (m, 3H), 5.06 (t, $J = 10.1$ Hz, 1H), 5.26 (t, $J = 9.2$ Hz, 1H), 5.36 (dd, $J = 9.7, 10.3$ Hz, 1H), 5.42 (d, $J = 4.2$ Hz, 1H), 7.43 (dd, $J = 2.2, 8.3$ Hz, 1H), 7.53 (d, $J = 8.3$
30 Hz, 1H), 7.83 (d, $J = 2.0$ Hz, 1H); IR (KBr) 3450, 2950, 1755, 1550, 1375, 1230 and 1050 cm^{-1} ; mass spectrum [(+) ESI], m/z 823/825 ($\text{M} + \text{NH}_4^+$), 828/830 ($\text{M} + \text{Na}^+$); Anal. Calcd. for $\text{C}_{33}\text{H}_{40}\text{ClNO}_{20}$: C, 49.17; H, 5.00; N, 1.74, Found: C, 49.16; H, 4.88; N, 1.71.

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Example 2

N-{5-[(Hepta-*O*-acetyl- β -D-maltosyloxy)-methyl]-2-chloro-phenyl}-L-aspartamide- γ -*tert*-butyl ester

step 1

2-Chloro-5-(hepta-*O*-acetyl- β -D-maltosyl-oxymethyl)-phenylamine

A solution containing 4-chloro-3-nitro-benzyl- β -D-maltoside heptaacetate (Example 1, 19.3 g, 23.9 mmol) and tin (II) chloride dihydrate (37.7 g, 167 mmol) in EtOAc (479 mL) was refluxed for 2 h. The reaction was cooled to rt, carefully quenched with sat. aq. NaHCO₃ (until basic), diluted with EtOAc (250 mL), stirred for 0.5 h and filtered. The biphasic filtrate was separated and the aqueous phase extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄) and concentrated. Purification by flash chromatography (0 to 12% acetone/CHCl₃ gradient) gave 17.8 g (96%) 2-Chloro-5-(hepta-*O*-acetyl- β -D-maltosyl-oxymethyl)-phenylamine as a glassy solid, mp 78-79 °C; ¹H NMR (CDCl₃) δ 2.00 (s, 9H), 2.026 (s, 3H), 2.032 (s, 3H), 2.11 (s, 3H), 2.16 (s 3H), 3.00-5.00 (bs, 2H), 3.64-3.68 (m, 1H), 3.97 (ddd, J = 2.4, 4.2, 10.1 Hz, 1H), 4.02-4.07 (m, 2H), 4.24 (dd, J = 2.2, 3.7, 1H), 4.27 (dd, J = 2.6, 4.0 Hz, 1H), 4.50-4.57 (m, 3H), 4.74 (d, J = 12.1 Hz, 1H), 4.83-4.90 (m, 2H), 5.05 (t, J = 10.1 Hz, 1H), 5.22 (t, J = 9.2 Hz, 1H), 5.35 (dd, J = 9.7, 10.5 Hz, 1H), 5.42 (d, J = 4.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.1 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 8.1, 1H); IR (KBr) 3450, 3350, 2950, 1755, 1650, 1425, 1375, 1230 and 1050 cm⁻¹; mass spectrum [(+) ESI], m/z 776/778 (M + H)⁺, 798/800 (M + Na)⁺; Anal. Calcd. for C₃₃H₄₂ClNO₁₈: C, 51.07; H, 5.45; N, 1.80, Found: C, 50.94; H, 5.52; N, 1.60.

step 2

N-{5-[(Hepta-*O*-acetyl- β -D-maltosyloxy)-methyl]-2-chloro-phenyl}-(9*H*-fluoren-9-ylmethoxycarbonylamino)-L-aspartamide-4-*tert*-butyl ester

To a stirred solution of *N*-(9*H*-fluoren-9-ylmethoxycarbonylamino)-L-aspartic acid-4-*tert*-butyl ester (0.117 g, 0.284 mmol) and DMF (cat. amt.) in CH₂Cl₂ (3 mL) at rt was added oxalyl chloride (24.8 μ L, 0.284 mmol) dropwise. After 5 min.

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at this temperature, it was heated to 40 °C for an additional 10 min. This completed the preparation of the acid chloride starting material. At this point, to a second stirred solution of NaH (0.0103 g, 0.258 mmol) and CH₂Cl₂ (4 mL) at rt was added 2-chloro-5-(hepta-*O*-acetyl-β-D-maltosyl-oxymethyl)-phenylamine (0.200 mg, 0.258 mmol).
5 After 10 min., the acid chloride solution was added to this solution dropwise. The reaction was stirred at rt for 1 h and then diluted with EtOAc (100 mL). This layer was washed with 1N HCl (10 mL), sat. NaHCO₃ (10 mL), and brine (10 mL) and then dried (MgSO₄). After concentration, the oily residue was purified by flash chromatography (10:90 to 70:30 EtOAc:petroleum ether gradient) to afford the
10 product (0.157 g, 52%) as a white foam, mp 103-105 °C; ¹H NMR (CDCl₃) δ 1.46 (s, 9H), 1.99 (s, 3H), 2.00 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 2.10 (s, 3H), 2.16 (s, 3H), 2.70 (dd, J = 5.9, 17.4 Hz, 1H), 2.96-3.06 (m, 1H), 3.67 (ddd, J = 2.6, 4.2, 9.7 Hz, 1H), 3.96 (ddd, J = 2.4, 3.7, 10.3 Hz, 1H), 4.00-4.06 (m, 2H), 4.22-4.28 (m, 3H), 4.42-4.48 (m, 1H), 4.48-4.56 (m, 2H), 4.58 (dd, J = 2.2, 10.1 Hz, 2H), 4.68-
15 4.76 (m, 1H), 4.81-4.91 (m, 3H), 5.05 (t, J = 10.1 Hz, 1H), 5.22 (t, J = 9.2 Hz, 1H), 5.35 (dd, J = 9.7, 10.5 Hz, 1H), 5.41 (d, J = 4.0 Hz, 1H), 6.07-6.15 (m, 1H), 7.00 (dd, J = 2.0, 8.1 Hz, 1H), 7.28-7.36 (m, 3H), 7.40 (t, J = 7.2 Hz, 2H), 7.57-7.62 (m, 2H), 7.77 (d, J = 7.5 Hz, 2H), 8.31 (d, J = 1.8 Hz, 1H), 8.86 (s, 1H); IR (KBr) 3380, 2960, 1755, 1600, 1540, 1440, 1420, 1375, 1230, 1160, and 1050 cm⁻¹; mass spectrum [(+) FAB], m/z 1169 (M + H)⁺, 1191 (M + Na)⁺; Anal. Calcd. for C₅₆H₆₅ClN₂O₂₃ · 2.0 H₂O: C, 55.79; H, 5.77; N, 2.32, Found: C, 55.89; H, 5.45; N, 2.25.
20

step 3

***N*-{5-[(Hepta-*O*-acetyl-β-D-maltosyloxy)-methyl]-2-chloro-phenyl}-L-aspartamide-γ-*tert*-butyl ester**
25

To a stirred solution of 20% piperidine (2.00 mL, 20.2 mmol) in DMF (10 mL) at rt was added *N*-{5-[(hepta-*O*-acetyl-β-D-maltosyloxy)-methyl]-2-chloro-phenyl}-(9*H*-fluoren-9-ylmethoxycarbonylamino)-L-aspartamide-4-*tert*-butyl ester (0.300 g, 0.256 mmol). After 1 h at this temperature, the solution was concentrated
30 on the high vacuum. At this point, the residue was diluted with cold H₂O (20 mL) and then extracted with Et₂O (50 mL). This layer was dried (Na₂SO₄) and after concentration, the resulting oil was purified by flash chromatography (20:80 to 90:10

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EtOAc:petroleum ether gradient) to afford the product (0.186 g, 77%) as a white solid, mp 85-87 °C; ¹H NMR (CDCl₃) δ 1.45 (s, 9H), 1.89 (s, 2H), 1.99 (s, 6H), 2.01 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 2.10 (s, 3H), 2.16 (s, 3H), 2.68 (dd, J = 8.1, 16.7 Hz, 1H), 2.91 (dd, J = 3.7, 16.7 Hz, 1H), 3.64-3.69 (m, 1H), 3.80 (dd, J = 3.7, 8.3 Hz, 1H), 3.93-3.98 (m, 1H), 3.99-4.05 (m, 2H), 4.21-4.27 (m, 2H), 4.50 (dd, J = 2.6, 12.1 Hz, 1H), 4.56 (d, J = 3.7 Hz, 1H), 4.59 (d, J = 8.1 Hz, 1H), 4.81-4.91 (m, 3H), 5.05 (t, J = 10.1 Hz, 1H), 5.22 (t, J = 9.4 Hz, 1H), 5.34 (dd, J = 9.4, 10.3 Hz, 1H), 5.40 (d, J = 4.0 Hz, 1H), 6.98 (dd, J = 2.0, 8.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 8.42 (d, J = 2.0 Hz, 1H), 10.28 (s, 1H); IR (KBr) 3380, 2960, 1755, 1600, 1540, 1440, 1420, 1375, 1235, 1140, and 1040 cm⁻¹; mass spectrum [(+) FAB], m/z 947/949 (M + H)⁺, 969/971 (M + Na)⁺; Anal. Calcd. for C₄₁H₅₅ClN₂O₂₁: C, 51.98; H, 5.85; N, 2.96, Found: C, 51.62; H, 5.89; N, 2.95.

Example 3

N-{2-Chloro-5-[(2,2',3,3',4',6,6')-hepta-*O*-acetyl-β-D-maltosyl-oxymethyl]-phenyl}-(9*H*-fluoren-9-ylmethoxycarbonyl)-L-alaninamide

The title compound was prepared as a white foam (2.50 g, 36%) from 2-chloro-5-(hepta-*O*-acetyl-β-D-maltosyl-oxymethyl)-phenylamine using *N*-(9*H*-fluoren-9-ylmethoxycarbonylamino)-L-alanine and a procedure similar to step 2 of **Example 2**, mp >96 °C (decomp.); ¹H NMR (DMSO-*d*₆) δ 1.33 (dd, J = 7.2 Hz, 3H), 1.918 (s, 3H), 1.919 (s, 3H), 1.94 (s, 3H), 1.966 (s, 3H), 1.97 (s, 3H), 2.01 (s, 3H), 2.07 (s, 3H), 3.91-4.02 (m, 4H), 4.12-4.24 (m, 3H), 4.24-4.34 (m, 3H), 4.34-4.40 (m, 1H), 4.53 (d, J = 12.7 Hz, 1H), 4.68-4.75 (m, 2H), 4.84 (d, J = 4.0 Hz, 1H), 4.86 (d, J = 2.6 Hz, 1H), 4.97 (t, J = 9.7 Hz, 1H), 5.21 (t, J = 9.7 Hz, 1H), 5.27 (d, J = 3.7 Hz, 1H), 5.27-5.32 (m, 1H), 7.08 (dd, J = 1.8, 8.1 Hz, 1H), 7.32 (t, J = 7.2 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.47 (d, J = 8.1 Hz, 1H), 7.69-7.78 (m, 4H), 7.88 (d, J = 7.5 Hz, 2H), 9.42 (s, 1H); IR (KBr) 3360, 3010, 2950, 1755, 1590, 1535, 1440, 1420, 1370, 1230, 1050, and 755 cm⁻¹; mass spectrum [(+) ESI], m/z 1069.2 (M + H)⁺, 1086.2/1088.2 (M + NH₄)⁺; Anal. Calcd. for C₅₁H₅₇ClN₂O₂₁ · 3.5 H₂O: C, 54.09; H, 5.70; N, 2.47, Found: C, 53.67; H, 5.11; N, 2.34.

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Example 4

4-Benzoyl-N-{2-chloro-5-[(2,2',3,3',4',6,6'-hepta-O-acetyl- β -D-maltosyl)-oxymethyl]-phenyl}-benzamide

5 The title compound was prepared as a white foam (0.240 g, 94%) from 2-chloro-5-(hepta-O-acetyl- β -D-maltosyl-oxymethyl)-phenylamine using *p*-benzoylbenzoic acid and a procedure similar to step 2 of **Example 2**, mp >84 °C (decomp.); ¹H NMR (DMSO-*d*₆) δ 1.93 (s, 3H), 1.94 (s, 6H), 1.97 (s, 6H), 2.01 (s, 3H), 2.08 (s, 3H), 3.93-4.03 (m, 4H), 4.15 (dd, J = 4.6, 12.3 Hz, 1H), 4.21 (dd, J =
10 4.6, 12.1 Hz, 1H), 4.39 (dd, J = 2.2, 11.9 Hz, 1H), 4.70 (ABq, J = 12.7 Hz, $\Delta\delta$ = 0.14, 2H), 4.74 (dd, J = 8.1, 9.7 Hz, 1H), 4.86 (dd, J = 4.0, 10.5 Hz, 1H), 4.90 (d, J = 8.1 Hz, 1H), 4.98 (t, J = 9.7 Hz, 1H), 5.21 (dd, J = 9.7, 10.5 Hz, 1H), 5.28 (d, J = 4.0 Hz, 1H), 5.31 (dd, J = 8.6, 9.4 Hz, 1H), 7.22 (dd, J = 2.0, 8.3 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.55-7.62 (m, 3H), 7.69-7.74 (m, 1H), 7.76-7.80 (m, 2H), 7.85-7.88 (m,
15 2H), 8.11-8.14 (m, 2H), 10.30 (s, 1H); IR (KBr) 3400, 3010, 2950, 1755, 1675, 1650, 1590, 1530, 1440, 1420, 1370, 1230, 1130, and 1040 cm⁻¹; mass spectrum [(+) FAB], m/z 984/986 (M + H)⁺, 1006/1008 (M + Na)⁺; Anal. Calcd. for C₃₇H₅₀ClNO₂₀: C, 57.35; H, 5.12; N, 1.42, Found: C, 57.11; H, 5.03; N, 1.32.

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Example 5

(4-Chloro-3-nitro-benzyl)-hepta-O-acetyl-1-thio-β-D-maltoside

To a stirred solution of hepta-O-acetyl-1-thio-β-maltose (2.0 g, 3.065 mmol) [P. L. Durette; T. Y. Shen. *Carb. Res.* 1978, 67, 484-490.] in acetone (20 ml) were
5 added 4-chloro-3-nitrobenzyl bromide (0.844 mg, 3.37 mmol) and a solution of potassium carbonate (0.423 mg, 3.065 mmol) in water (10 ml). The mixture was boiled under reflux for 30 min, cooled and concentrated. The residue was extracted with dichloromethane, and the combined extracts were washed with water, and brine, dried (MgSO₄) and concentrated. Purification by flash chromatography (40%-60%
10 EtOAc/petroleum ether gradient) afforded 1.588 g (63%) of the title compound as a white solid, mp 73-75 °C; ¹H NMR (CDCl₃) δ 1.99 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.03 (s, 6H), 2.11 (s, 3H), 2.15 (s, 3H), 3.61-3.64 (m, 1H), 3.80 (d, J = 13.6 Hz, 1H), 3.94 - 4.00 (m, 3H), 4.08 (dd, J = 12.3, 2.4 Hz, 1H), 4.18-4.27 (m, 2H), 4.36 (d, J = 9.9 Hz, 1H), 4.50 (dd, J = 12.1, 2.6 Hz, 1H), 4.85 (dd, J = 10.5, 4.0 Hz, 1H), 4.90
15 (apparent t, J = 9.9 Hz, 1H), 5.05 (apparent t, J = 9.9 Hz, 1H), 5.23 (apparent t, J = 9.2 Hz, 1H), 5.34 (apparent t, J = 9.7 Hz, 1H), 5.40 (d, J = 4.0 Hz, 1H), 7.47 (dd, J = 8.4, 2.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 2.0, Hz, 1H); IR (KBr) 3500, 2950, 1750, 1250 and 1050 cm⁻¹; mass spectrum [(+) FAB], m/z 822 (M + H)⁺, 844 (M + Na)⁺; Anal. Calcd. for C₃₃H₄₀ClNO₁₉S: C, 48.21; H, 4.90; N, 1.70, Found: C, 47.75; H, 4.86; N, 1.65.
20

Example 6

(3-Amino-4-chloro-benzyl) hepta-O-acetyl-1-thio-β-D-maltoside

25 The title compound was prepared as a white solid from (4-chloro-3-nitro-benzyl)-hepta-O-acetyl-1-thio-β-D-maltoside using a procedure similar to step 1 of Example 2, mp 78 °C; ¹H NMR (CDCl₃) δ 1.99 (s, 9H), 2.02 (s, 3H), 2.03 (s, 3H), 2.11 (s, 3H), 2.18 (s, 3H), 3.57-3.60 (m, 1H), 3.73 (ABq, J = 13.0 Hz, Δδ = 0.16, 2H), 3.95-4.08 (m, 3H), 4.17 (bs, 2H), 4.23 (d, J = 4.2, Hz, 2H), 4.27 (dd, J = 7.7, 4.4 Hz,
30 1H), 4.31 (d, J = 4.4, Hz, 1H), 4.34 (d, J = 10.1, Hz, 1H),), 4.44 (dd, J = 12.1, 3.3 Hz, 1H),), 4.84 (dd, J = 10.5, 4.0 Hz, 1H), 4.88 (apparent t, J = 9.9 Hz, 1H), 5.03 (apparent t, J = 9.9 Hz, 1H), 5.35 (apparent t, J = 9.0 Hz, 1H), 5.35 (apparent t, J =

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9.4 Hz, 1H), 5.40 (d, J = 4.0, Hz, 2H), 6.60 (dd, J = 8.1, 2.0 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 8.13 Hz, 1H); IR (KBr) 3500, 2950, 1750, 1245 and 1050 cm^{-1} ; mass spectrum [(-) FAB], m/z 790 (M - H); Anal. Calcd. for $\text{C}_{33}\text{H}_{42}\text{ClNO}_{17}$: C, 50.03; H, 5.34; N, 1.77, Found: C, 49.55; H, 5.21; N, 1.71.

5

Example 7

N-{2-Chloro-5-[hepta-O-acetyl- β -D-maltosyl-1-thio)-methyl]-phenyl}-acetamide

The title compound was prepared as a white solid from (3-amino-4-chloro-
10 benzyl) hepta-O-acetyl-1-thio- β -D-maltoside using a procedure similar to step 1 of
Example 9, mp 80-81 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.99 (s, 9H), 2.03 (s, 6H), 2.11 (s, 3H),
2.16 (s, 3H), 2.25 (s, 3H), 3.61-3.65 (m, 1H), 3.82 (ABq, J = 13.2 Hz, $\Delta\delta$ = 0.14, 2H),
3.94-4.11 (m, 3H), 4.34 (d J = 10.1 Hz, 1H), 4.53 (dd, J = 12.3, 2.6 Hz, 1H), 4.83-
4.91 (m, 2H), 5.05 (apparent t, J = 9.7 Hz, 1H), 5.20 (apparent t, J = 9.0 Hz, 1H),
15 5.34 (apparent t, J = 10.3 Hz, 1H), 5.39 (d, J = 4.2 Hz, 1H), 7.00 (dd, J = 8.1, 2.2 Hz,
1H), 7.33 (d, J = 8.4 Hz, 1H), 7.62 (s, 1H), 8.31 (s, 1H); IR (KBr) 3400, 2955, 1750,
1245 and 1050 cm^{-1} ; mass spectrum [(+) FAB], m/z 834 (M + H) $^{+}$, 856 (M + Na) $^{+}$;
Anal. Calcd. for $\text{C}_{35}\text{H}_{44}\text{ClNO}_{18}$: C, 50.39; H, 5.32; N, 1.68, Found: C, 49.99; H,
5.07; N, 1.59 .

20

Example 8

5-[(Hepta-O-acetyl- β -D-maltosyl)-oxy-methyl]-2-cyano-1-nitrobenzene

step 1

25 α -Bromo-2-nitro-*p*-tolunitrile

A stirred mixture containing 4-methyl-2-nitrobenzonitrile (2.04 g, 12.6
mmol), N-bromosuccinimide (2.24 g, 12.6 mmol) and azobisisobutyronitrile (0.103
g, 0.630 mmol) in CCl_4 (50 mL) was irradiated with a 300 watt flood light for 2 h.
The reaction was diluted with CH_2Cl_2 (50 ml), filtered and concentrated. Purification
30 by flash chromatography (35 and 40% ether/pet. ether gradient) gave 1.44 g (47%) of
the title compound as a yellow oil. ^1H NMR ($\text{DMSO}-d_6$) δ 4.90 (s, 2H), 8.05 (dd, J =
8.0, 1.5 Hz, 1H), 8.18 (d, J = 8.0, 1H), 8.52 (s, 1H).

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step 2

α -Hydroxy-2-nitro-*p*-tolunitrile

A stirred solution containing α -bromo-2-nitro-*p*-tolunitrile (1.228 g, 5.095 mmol) and sodium formate (0.8664 g, 12.74 mmol) in ethanol:water (4:1, 25 mL) was refluxed for 2 h. The reaction was cooled to room temperature, diluted with 20% CH₂Cl₂/EtOAc, washed with H₂O (3x), dried (MgSO₄) and concentrated. Purification by flash chromatography (1,2 and 3% MeOH/CHCl₃ gradient) gave 0.695 g (77%) of the title compound as a white solid. ¹H NMR (DMSO-*d*₆) δ 4.71 (d, 2H), 5.75 (t, 1H), 7.89 (dd, J = 7.9 Hz, 1H), 8.14 (d, J = 7.9 Hz, 1H), 8.32 (s, 1H).

step 3

5-[(Hepta-*O*-acetyl- β -D-maltosyl)-oxy-methyl]-2-cyano-1-nitrobenzene

At ambient temperature, to a stirred solution of acetobromomaltose (2.39 g, 3.41 mmol), α -hydroxy-2-nitro-*p*-tolunitrile (0.789 g, 4.43 mmol) and HgBr₂ (1.60 g, 4.43 mmol) in freshly distilled CH₃CN (34 mL) was added in one portion Hg(CN)₂ (1.12 g, 4.43 mmol). After 16 h, brine (50 mL) was added and the mixture was extracted with 10% CH₂Cl₂/EtOAc. The combined organic extracts were washed with brine (3x), dried (MgSO₄) and concentrated. Purification by flash chromatography (1,2 and 3% MeOH/CHCl₃ gradient) gave 1.941 g (71%) of the title compound as a foam. An analytical sample was obtained by recrystallization from EtOAc/Hexane followed by recrystallization from EtOH to give a white solid, mp 155-157 °C; ¹H NMR (DMSO-*d*₆) δ 1.93 (s, 3H), 1.94 (s, 3H), 1.97 (s, 3H), 1.99 (s, 3H), 2.01 (s, 3H), 2.06 (s, 3H), 3.93-4.01 (m, 4H), 4.36 (d, J = 11.0 Hz, 1H), 4.77 (dd, J = 9.6, 8.0 Hz, 1H), 4.83-4.88 (m, 2H), 4.93-5.00 (m, 3H), 5.21 (dd, J = 10.3, 9.7 Hz, 1H), 5.27 (d, J = 3.7 Hz, 1H), 5.30-5.34 (m, 1H), 7.84 (dd, J = 7.9, 1.5 Hz, 1H), 8.18 (d, J = 7.9 Hz, 1H), 8.27 (s, 1H); IR (KBr) 3450, 2950, 2225, 1750, 1225 and 1050 cm⁻¹; mass spectrum [(+) FAB], *m/z* 797 (M + H)⁺; Anal. Calcd. for C₃₄H₄₀N₂O₂₀: C, 51.26; H, 5.06; N, 3.52, Found: C, 51.06; H, 5.02; N, 3.31.

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Example 9

N-[2-Chloro-5-(β -D-maltosyl-oxymethyl)-phenyl]-acetamide

step 1

N-[2-Chloro-5-(hepta-O-acetyl- β -D-maltosyl-oxymethyl)-phenyl]-

- 5 To a stirred solution of 2-chloro-5-(hepta-O-acetyl- β -D-maltosyl-oxymethyl)-phenylamine (20.6 g, 26.5 mmol) and triethylamine (8.13 mL, 58.3 mmol) in THF (265 mL) at 0 °C was added dropwise acetyl chloride (2.26 mL, 31.8 mmol). After 0.5 h at this temperature, it was warmed to rt and stirred an additional 6 h. At this point, the reaction was concentrated and taken up in EtOAc (700 mL). This organic
- 10 solution was washed with 1 N HCl (70 mL), sat. aq. NaHCO₃ (70 mL), and brine (70 mL) and then dried (MgSO₄). After concentration, the residue was purified by flash chromatography (20:80 to 100:0 EtOAc:petroleum ether gradient) to afford the product (16.2 g, 75%) as a glassy solid, mp 84-86 °C; ¹H NMR (CDCl₃) δ 2.00 (s, 6H), 2.020 (s, 3H), 2.027 (s, 3H), 2.03 (s, 3H), 2.11 (s, 3H), 2.16 (s, 3H), 2.24 (s,
- 15 3H), 3.66-3.69 (m, 1H), 3.94-3.98 (m, 1H), 4.00-4.06 (m, 2H), 4.22-4.28 (m, 2H), 4.50-4.61 (m, 3H), 4.80-4.91 (m, 3H), 5.05 (t, J = 10.1 Hz, 1H), 5.22 (t, J = 9.2 Hz, 1H), 5.35 (dd, J = 9.4, 10.5 Hz, 1H), 5.41 (d, J = 4.0 Hz, 1H), 6.99 (dd, J = 2.0, 8.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.62 (s, 1H), 8.32 (s, 1H); IR (KBr) 3400, 2950, 1750, 1690, 1600, 1540, 1425, 1375, 1230 and 1050 cm⁻¹; mass spectrum [(+) ESI],
- 20 m/z 818/820 (M + H)⁺, 840 (M + Na)⁺; Anal. Calcd. for C₃₅H₄₄ClNO₁₉: C, 51.38; H, 5.42; N, 1.71, Found: C, 51.03; H, 5.36; N, 1.59.

step 2

N-[2-Chloro-5-(β -D-maltosyl-oxymethyl)-phenyl]-acetamide

- 25 A solution containing N-[2-chloro-5-(hepta-O-acetyl- β -D-maltosyl-oxymethyl)-phenyl]-acetamide (0.945 g, 1.12 mmol) and 25 weight % NaOMe in MeOH (19.2 μ L, 0.336 mmol) in MeOH (27.6 ml) was refluxed for 2.5 h. The reaction was cooled to room temperature and concentrated, and the resulting residue was triturated with Et₂O to afford the product (0.583 g, 99%) as a foam; ¹H NMR
- 30 (DMSO-*d*₆) δ 2.07 (s, 3H), 3.03-3.16 (m 2H), 3.19-3.49 (m, 7H), 3.55-3.62 (m, 2H), 3.67-3.73 (m, 1H), 4.28 (d, J = 7.7 Hz, 1H), 4.33-5.76 (bs, 7H), 4.67 (ABq, J = 12.5 Hz, $\Delta\delta$ = 0.22, 2H), 5.01 (d, J = 3.7 Hz, 1H), 7.21 (dd, J = 1.8, 8.1 Hz, 1H), 7.44 (d, J

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= 8.1 Hz, 1H), 7.64 (d, J = 1.5 Hz, 1H), 9.33-9.69 (bs, 1H); IR (KBr) 3400, 2900, 1680, 1600, 1540, 1430, 1375, 1310, 1150 and 1035 cm^{-1} ; mass spectrum [(+) ESI], m/z 524/526 (M + H)⁺, 546 (M + Na)⁺; Anal. Calcd. for $\text{C}_{21}\text{H}_{30}\text{ClNO}_{12} \cdot 1.0 \text{ MeOH}$: C, 47.53; H, 6.16; N, 2.52, Found: C, 47.94; H, 6.34; N, 2.42.

5

Example 10

N -{5-[6,6'-Di-O-(tert-butyl-dimethyl-silyl)-β-D-maltosyloxy-methyl]-2-methyl-phenyl}-acetamide

10 To a stirred solution of N-[5-(β-D-maltosyl-oxymethyl)-2-methyl-phenyl]-acetamide (prepared from 4-methyl-3-nitrobenzyl alcohol and acetobromomaltose using procedures similar to **Example 1**, **Example 2**-step 1, and **Example 9**)(1.5 g, 2.98 mmol) in CH_2Cl_2 :DMF (1:1, 12 mL) at rt was added DMAP (0.109 g, 0.892 mmol) followed by triethylamine (1.66 mL, 11.9 mmol), and then finally TBDMSCl
15 (1.35 g, 8.96 mmol). After 18, the solvent was removed on high vac and the residue diluted with EtOAc (200 mL). This organic layer was washed with 1 N HCl (20 mL), sat. aq. NaHCO_3 (20 mL), and brine (20 mL) and then dried (MgSO_4). After concentration, the residue was purified by flash chromatography (0:100 to 25:75 MeOH: CHCl_3 gradient) to afford the product (16.2 g, 75%) as a white foam, mp 111-
20 114 °C; ^1H NMR (CDCl_3) δ 0.067 (s, 6H), 0.080 (s, 3H), 0.084 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 2.07 (s, 3H), 2.16 (s, 3H), 3.25-3.28 (m, 1H), 3.34-3.38 (m, 1H), 3.45-3.52 (m, 3H), 3.65-3.78 (m, 4H), 3.84-3.94 (m, 4H), 4.28 (d, J = 7.7 Hz, 1H), 4.64 (ABq, J = 12.1 Hz, $\Delta\delta$ = 0.27, 2H), 4.65-4.69 (bs, 1H), 4.74-4.78 (m, 1H), 4.97 (d, J = 3.3 Hz, 1H), 5.25-5.30 (m, 1H), 5.63-5.68 (bs, 1H), 6.99 (d, J = 7.9 Hz, 1H), 7.07
25 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.59-7.63 (bs, 1H); IR (KBr) 3400, 2930, 2870, 1670, 1600, 1550, 1450, 1375, 1255, 1125, 1050, 840, and 790 cm^{-1} ; mass spectrum [(+) FAB], m/z 754 (M + Na)⁺; Anal. Calcd. for $\text{C}_{34}\text{H}_{61}\text{NO}_{12}\text{Si}_2 \cdot 0.5 \text{ H}_2\text{O}$: C, 55.11; H, 8.43; N, 1.89, Found: C, 54.91; H, 8.36; N, 1.85.

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Example 11

N-[2-Chloro-5-[6,6'-di-*O*-(*tert*-butyl-dimethyl-silyl)- β -D-maltosyloxy-methyl]-phenyl]-acetamide

The title compound was prepared as a white foam (0.845 g, 59%) from *N*-[2-chloro-5-(β -D-maltosyl-oxymethyl)-phenyl]-acetamide using a procedure similar to **Example 10**, mp 93-98 °C; ^1H NMR (CDCl_3) δ 0.07 (s, 12H), 0.88 (s, 9H), 0.89 (s, 9H), 2.18 (s, 3H), 3.25-3.31 (m, 1H), 3.41-3.46 (m, 1H), 3.49-3.58 (m, 3H), 3.69-3.79 (m, 4H), 3.85 (d, J = 4.0 Hz, 1H), 3.87-3.92 (m, 2H), 3.92 (d, J = 2.6 Hz, 1H), 4.32 (d, J = 7.7 Hz, 1H), 4.53-4.58 (m, 1H), 4.68 (ABq, J = 12.5 Hz, $\Delta\delta$ = 0.25, 2H), 4.71-4.75 (m, 1H), 5.00 (d, J = 3.5 Hz, 1H), 5.25 (dd, J = 2.0, 6.4 Hz, 1H), 5.69 (s, 1H), 6.98-7.04 (m, 1H), 7.25-7.29 (m, 1H), 7.66 (s, 1H), 8.25 (s, 1H); IR (KBr) 3400, 2930, 2880, 1675, 1600, 1550, 1460, 1420, 1365, 1250, 1050, 850, and 800 cm^{-1} ; mass spectrum [(+) FAB], m/z 774/776 ($M + \text{Na}$) $^+$; Anal. Calcd. for $\text{C}_{33}\text{H}_{58}\text{ClNO}_{12}\text{Si}_2 \cdot 0.5 \text{H}_2\text{O}$: C, 52.05; H, 7.81; N, 1.84, Found: C, 52.16; H, 7.82; N, 1.80.

Example 12

N-[2-Chloro-5-[[6,6'-di-*O*-benzoyl- β -D-maltosyl]oxy)methyl]phenyl]-acetamide

To a stirred solution of *N*-[2-chloro-5-(β -D-maltosyl-oxymethyl)-phenyl]-acetamide (1.00 g, 1.91 mmol) in THF (20.0 mL) at -40 °C was added collidine (20.0 mL, 151 mmol) followed by dropwise addition of benzoyl chloride (0.532 mL, 4.58 mmol). After 2 h at this temperature, it was warmed to rt and stirred an additional 18 h. At this point, the solvent was distilled off using the high vac, and the residue was purified by flash chromatography (2% to 20% MeOH: CHCl_3 gradient) to afford the product (0.500 g, 36%) as a glassy white solid, mp 99-100 °C; ^1H NMR (CDCl_3) δ 2.12 (s, 3H), 3.41-3.51 (m, 3H), 3.59-3.68 (m, 2H), 3.77 (t, J = 9.2 Hz, 1H), 3.85 (t, J = 9.2 Hz, 1H), 4.06-4.12 (m, 1H), 4.30-4.34 (m, 2H), 4.40-5.35 (bs, 3H), 4.51 (dd, J = 5.3, 12.1 Hz, 1H), 4.57 (ABq, J = 12.5 Hz, $\Delta\delta$ = 0.22, 2H), 4.59 (d, J = 10.5 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 5.07 (d, J = 3.1 Hz, 1H), 5.45-5.66 (bs, 1H), 5.75-5.95 (bs, 1H), 6.86 (dd, J = 1.3, 8.3 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.23 (t, J = 7.7 Hz, 2H), 7.33-7.52 (m, 4H), 7.70 (s, 1H), 7.91-7.96 (m, 4H), 8.14 (s, 1H); IR (KBr)

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3400, 2900, 1720, 1620, 1600, 1550, 1450, 1425, 1375, 1320, 1225, 1100, and 1060 cm^{-1} ; mass spectrum [(+) FAB], m/z 732 ($M + H$)⁺, 754 ($M + Na$)⁺; Anal. Calcd. for $C_{35}H_{38}ClNO_{14} \cdot 0.5 H_2O$: C, 56.72; H, 5.30; N, 1.89, Found: C, 56.62; H, 5.04; N, 1.90.

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Example 13

N-{2-Chloro-5-[(6,6'-di-*O*-benzoyl-2,2',3,3',4'-penta-acetyl- β -D-maltosyl]oxy)methyl]phenyl}-acetamide

10 To a stirred solution of *N*-{5-[(6,6'-di-*O*-benzoyl- β -D-maltosyl]oxy)methyl}-2-chlorophenyl}-acetamide (0.122 g, 0.167 mmol) and triethylamine (0.256 mL, 1.84 mmol) in CH_2Cl_2 (5.0 mL) at rt was added dropwise acetic anhydride (0.0865 mL, 0.916 mmol) followed by a catalytic amount of DMAP (0.0102 g, 0.0835 mmol). After 18 h, the mixture was diluted with EtOAc (50 mL). This layer was washed with
15 1 N HCl (5 mL), sat. aq. $NaHCO_3$ (5 mL), and brine (5 mL) and then dried ($MgSO_4$). After concentration, the residue was purified by flash chromatography (2% to 20% acetone: $CHCl_3$ gradient) to afford the product (1.68 g, 94%) as a fine white powder (0.120 g, 76%), mp 97-100 °C; 1H NMR ($CDCl_3$) δ 1.96 (s, 3H), 1.99 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.22 (s, 3H), 3.80-3.84 (m, 1H), 4.06-4.10 (m, 1H),
20 4.18-4.22 (m, 3H), 4.53 (dd, $J = 4.0, 12.3$ Hz, 1H), 4.58 (d, $J = 9.7$ Hz, 1H), 4.61 (d, $J = 5.1$ Hz, 1H), 4.76-4.79 (m, 1H), 4.79-4.82 (m, 1H), 4.86 (dd, $J = 4.0, 10.5$ Hz, 1H), 4.92 (dd, $J = 7.7, 9.2$ Hz, 1H), 5.15 (t, $J = 9.9$ Hz, 1H), 5.27 (t, $J = 9.0$ Hz, 1H), 5.41 (dd, $J = 9.7, 10.3$ Hz, 1H), 5.47 (d, $J = 4.2$ Hz, 1H), 6.95 (dd, $J = 1.8, 8.1$ Hz, 1H), 7.29 (d, $J = 8.3$ Hz, 1H), 7.41-7.50 (m, 4H), 7.52-7.62 (m, 3H), 7.98-8.01 (m,
25 2H), 8.07-8.09 (m, 2H), 8.30 (s, 1H); IR (KBr) 3400, 2950, 1760, 1725, 1620, 1600, 1550, 1450, 1425, 1375, 1275, 1245, 1120, 1050, and 710 cm^{-1} ; mass spectrum [(+) FAB], m/z 942 ($M + H$)⁺, 964 ($M + Na$)⁺; Anal. Calcd. for $C_{45}H_{48}ClNO_{19} \cdot 2.0 H_2O$: C, 55.25; H, 5.36; N, 1.43, Found: C, 55.18; H, 4.87; N, 1.36.

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Example 14

(4-Chloro-3-nitrophenyl)methyl-4-O-[6-O-(3-pyridinylcarbonyl)- α -D-glucopyranosyl]- β -D-glucopyranoside-6-(3-pyridinecarboxylate)

To a stirred solution of *N*-[2-chloro-5-(β -D-maltosyl-oxymethyl)-phenyl]-acetamide (0.500 g, 0.977 mmol) in THF (9.8 mL) at -40 °C was added collidine (9.8 mL, 74.3 mmol) dropwise followed by nicotinoyl chloride hydrochloride (0.417 g, 2.34 mmol). After 2 h at this temperature, it was warmed to rt and stirred an additional 42 h. At this point, the reaction was concentrated on high vacuum and then diluted with EtOAc (250 mL). The solid was filtered off and washed with additional EtOAc (50 mL). The filtrate was concentrated, and the resulting oily residue purified by flash chromatography (40:2:1 to 10:2:1 EtOAc:EtOH:H₂O gradient) to afford the product (0.159 g, 23%) as a white solid, mp 145-147 °C; ¹H NMR (DMSO-*d*₆) δ 3.15-3.25 (m, 2H), 3.32-3.35 (m, 1H), 3.43 (dd, *J* = 5.3, 9.2 Hz, 1H), 3.45-3.52 (m, 1H), 3.54 (t, *J* = 8.8 Hz, 1H), 3.70-3.76 (m, 1H), 3.91 (ddd, *J* = 1.3, 5.5, 9.7 Hz, 1H), 4.29-4.38 (m, 2H), 4.41 (d, *J* = 7.7 Hz, 1H), 4.53-4.58 (m, 1H), 4.67-4.72 (m, 1H), 4.72 (ABq, *J* = 13.6 Hz, $\Delta\delta$ = 0.07, 2H), 5.11 (d, *J* = 4.8 Hz, 2H), 5.35 (d, *J* = 5.7 Hz, 1H), 5.42 (d, *J* = 5.1 Hz, 1H), 5.70 (d, *J* = 2.6 Hz, 1H), 5.74 (d, *J* = 5.9 Hz, 1H), 7.42 (ddd, *J* = 0.6, 4.8, 7.9 Hz, 1H), 7.50 (ddd, *J* = 0.7, 4.8, 7.9 Hz, 1H), 7.62 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 1.8 Hz, 1H), 8.16 (tt, *J* = 2.0, 8.6 Hz, 2H), 8.66 (dd, *J* = 1.8, 4.8 Hz, 1H), 8.77 (dd, *J* = 1.8, 4.8 Hz, 1H), 8.97 (dt, *J* = 1.3, 9.2 Hz, 2H); IR (KBr) 3480, 3390, 3110, 2900, 1725, 1590, 1550, 1475, 1420, 1390, 1360, 1340, 1285, 1175, 1140, 1090, 1050, and 1015 cm⁻¹; mass spectrum [(+) FAB], *m/z* 722/724 (*M* + H)⁺, 744/746 (*M* + Na)⁺; Anal. Calcd. for C₃₁H₃₂ClN₃O₁₅ · 1.5 H₂O: C, 49.71; H, 4.71; N, 5.61, Found: C, 49.68; H, 4.53; N, 5.59.

Example 15

(4-Chloro-3-nitrophenyl)methyl-4-O-[6-O-(3-pyridinylcarbonyl)- α -D-glucopyranosyl]- β -D-glucopyranoside

The title compound was prepared as a white glass (0.070 g, 10%) from *N*-[2-chloro-5-(β -D-maltosyl-oxymethyl)-phenyl]-acetamide using a procedure similar to Example 14, mp >85 °C (decomp.); ¹H NMR (DMSO-*d*₆) δ 3.07-3.14 (m, 1H), 3.14-

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3.23 (m, 1H), 3.25-3.36 (m, 2H), 3.36-3.47 (m, 3H), 3.51-3.58 (m, 1H), 3.67-3.73 (m, 1H), 3.83-3.89 (m, 1H), 4.29-4.34 (m, 2H), 4.54-4.62 (m, 2H), 4.79 (ABq, J = 13.4 Hz, $\Delta\delta$ = 0.17, 2H), 5.05-5.08 (m, 2H), 5.31 (d, J = 5.7 Hz, 1H), 5.34 (d, J = 5.1 Hz, 1H), 5.56 (d, J = 6.4 Hz, 1H), 5.59 (d, J = 3.1 Hz, 1H), 7.56 (ddd, J = 0.9, 4.8, 8.1 Hz, 1H), 7.71 (dd, J = 2.0, 8.3 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 8.09 (d, J = 1.5 Hz, 1H), 8.33 (dt, J = 1.8, 7.9 Hz, 1H), 8.81 (dd, J = 1.8, 4.8 Hz, 1H), 9.10 (dd, J = 0.7, 2.0 Hz, 1H); IR (KBr) 3390, 2910, 1730, 1625, 1600, 1540, 1475, 1410, 1360, 1290, 1140, 1120, and 1040 cm^{-1} ; mass spectrum [(+) FAB], m/z 617/619 (M + H)⁺; Anal. Calcd. for $\text{C}_{25}\text{H}_{29}\text{ClN}_2\text{O}_{14} \cdot 1.5 \text{H}_2\text{O}$: C, 46.63; H, 5.01; N, 4.35, Found: C, 46.58; H, 4.88; N, 4.26.

Example 16

N-[2-Chloro-5-[[[(4-O- α -D-glucopyranosyl- β -D-glucopyranosyl)oxy]methyl]phenyl]-3-pyridinecarboxamide

step 1

N-[2-Chloro-5-[[[2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)- β -D-glucopyranosyl]oxy]methyl]phenyl]-3-pyridinecarboxamide

To a stirred solution of 2-chloro-5-(hepta-O-acetyl- β -D-maltosyl-oxymethyl)-phenylamine (0.200 g, 0.258 mmol) and triethylamine (0.119 mL, 0.851 mmol) in THF (3 mL) at 0 °C was added nicotinoyl chloride hydrochloride (0.0551 mg, 0.310 mmol). After 0.5 h at this temperature, it was warmed to rt and stirred an additional 18 h. At this point, the solid was filtered off and washed with additional THF (10 mL). The filtrate was then concentrated and taken up in EtOAc (100 mL). This organic solution was washed with H_2O (10 mL) and brine (10 mL) and then dried (Na_2SO_4). After concentration, the residue was purified by preparatory plate chromatography (10:90 MeOH: CHCl_3) to afford the product (0.183 g, 80%) as a white foam, mp 83-86 °C; ^1H NMR (CDCl_3) δ 1.99 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.10 (s, 3H), 2.16 (s, 3H), 3.67-3.72 (m, 1H), 3.93-3.98 (m, 1H), 4.04 (dd, J = 2.2, 11.9 Hz, 2H), 4.25 (dt, J = 3.7, 12.5 Hz, 2H), 4.53 (dd, J = 2.9, 12.3 Hz, 1H), 4.60 (d, J = 7.7 Hz, 1H), 4.64 (d, J = 12.5 Hz, 1H), 4.83-4.93 (m, 3H), 5.05 (t, J = 10.1 Hz, 1H), 5.23 (t, J = 9.4 Hz, 1H), 5.34 (dd, J = 9.7, 10.5 Hz,

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1H), 5.41 (d, J = 4.2 Hz, 1H), 7.07 (dd, J = 2.0 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H),
7.48 (ddd, J = 0.9, 4.8, 7.9 Hz, 1H), 8.23 (ddd, J = 1.5, 2.2, 7.9 Hz, 1H), 8.43 (s, 1H),
8.48 (d, J = 2.0 Hz, 1H), 8.82 (dd, J = 1.5, 4.8 Hz, 1H), 9.15 (dd, J = 0.7, 2.2 Hz,
1H); IR (KBr) 3400, 2950, 1755, 1675, 1600, 1550, 1420, 1375, 1235, and 1050 cm⁻¹;
5 mass spectrum [(+) FAB], m/z 881 (M + H)⁺, 903 (M + Na)⁺; Anal. Calcd. for
C₃₉H₄₅ClN₂O₁₉ · 2.0 H₂O: C, 51.07; H, 5.38; N, 3.05, Found: C, 50.80; H, 4.83; N,
2.89.

step 2

10 ***N*-[2-Chloro-5-[[[(4-*O*-α-D-glucopyranosyl-β-D-glucopyranosyl)oxy]methyl]
phenyl]-3-pyridinecarboxamide**

The title compound was prepared as a white foam (1.97 g, 57%) from *N*-[2-chloro-5-[[[2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranosyl]oxy]methyl]phenyl]-3-pyridinecarboxamide using a procedure
15 similar to step 2 of **Example 9**, mp >106 °C (decomp.); ¹H NMR (DMSO-*d*₆) δ 3.02-
3.13 (m, 2H), 3.19-3.29 (m, 2H), 3.31-3.39 (m, 1H), 3.39-3.50 (m, 3H), 3.55-3.63
(m, 2H), 3.70-3.76 (m, 1H), 4.09 (q, J = 5.3 Hz, 1H), 4.31 (d, J = 7.9 Hz, 1H), 4.49-
4.55 (m, 2H), 4.60 (d, J = 12.5 Hz, 1H), 4.84-4.91 (m, 3H), 5.01 (d, J = 3.7 Hz, 1H),
5.26 (d, J = 5.1 Hz, 1H), 5.43 (d, J = 6.4 Hz, 1H), 5.52 (d, J = 3.1 Hz, 1H), 7.35 (dd,
20 J = 2.0, 8.3 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.56-7.60 (m, 2H), 8.31 (dt, J = 2.0,
7.9 Hz, 1H), 8.77 (dd, J = 1.5, 4.8 Hz, 1H), 9.12-9.14 (m, 1H), 10.34 (s, 1H); IR
(KBr) 3390, 2910, 2320, 1660, 1590, 1525, 1475, 1450, 1420, 1360, 1310, 1190,
1140, 1080, and 1030 cm⁻¹; mass spectrum [(+) FAB], m/z 587 (M + H)⁺, 609 (M +
Na)⁺; Anal. Calcd. for C₂₅H₃₁ClN₂O₁₂ · 1.5 H₂O: C, 48.90; H, 5.58; N, 4.56, Found:
25 C, 49.18; H, 5.52; N, 4.32.

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Example 17

Benzoic acid 6-{4-chloro-3-[(pyridine-3-carbonyl)-amino]-benzyloxy}-4,5-dihydroxy-3-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-tetrahydro-pyran-2-ylmethyl ester hydrochloride

5 To a stirred solution of (R)-N-[5-[[[6-O-benzoyl-4-O-[4,6-O-(phenylmethylene)- α -D-glucopyranosyl]- β -D-glucopyranosyl]oxy]methyl]-2-chlorophenyl]-3-pyridinecarboxamide (check other invention record for preparation) (0.275 g, 0.353 mmol) in MeOH (10 mL) at 0 °C was added 1.0 M HCl in Et₂O (0.388 mL, 0.388 mmol). After 10 min. at this temperature, it was warmed to rt and
10 stirred an additional 15 min. The mixture was concentrated to a thin oil and then triturated with Et₂O (5 mL). At this point, the solid which formed was filtered off and washed with additional Et₂O (4x, 2 mL). The solid was then dried on the high vacuum to afford the product (0.200 g, 70%) as an off-white solid (86% pure, contaminated with 14% HCl salt of SM), mp >157 °C (decomp.); ¹H NMR (DMSO-*d*₆) δ 3.09-3.19 (m, 2H), 3.24 (dd, J = 3.7, 9.4 Hz, 1H), 3.34-3.41 (m, 1H), 3.41-3.65 (m, 5H), 3.71 (dd, J = 6.8, 8.1 Hz, 1H), 4.20-5.04 (m, 12H), 5.05 (d, J = 3.7 Hz, 1H), 7.28 (dd, J = 2.0, 8.3 Hz, 1H), 7.46-7.55 (m, 4H), 7.60-7.66 (m, 1H), 7.82 (dd, J = 5.1, 7.9 Hz, 1H), 7.94-7.99 (m, 2H), 8.58 (d, J = 7.7 Hz, 1H), 8.90 (dd, J = 1.5, 5.3 Hz, 1H), 9.23 (d, J = 1.5 Hz, 1H), 10.54 (s, 1H); IR (KBr) 3400, 2910, 2850, 2110,
15 1720, 1690, 1630, 1590, 1530, 1440, 1420, 1320, 1275, 1120, 1070, 1050, 1025, and 715 cm⁻¹; mass spectrum [(+) ESI], m/z 691.2 (M - HCl + H)⁺; Anal. Calcd. for C₃₂H₃₅ClN₂O₁₃ · HCl · 0.5 H₂O: C, 52.89; H, 5.06; N, 3.74, Found: C, 52.99; H, 5.27; N, 3.46.

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Example 18

(4-Chloro-3-nitro-benzyl)-1-deoxy-1-thio- β -D-maltoside

The title compound was prepared as a white solid from (4-chloro-3-nitro-benzyl)-hepta-O-acetyl-1-thio- β -D-maltoside using a procedure similar to step 2 of
30 **Example 9**, mp 90-93 °C; ¹H NMR (DMSO-*d*₆) δ 3.03-3.74 (m, , 11H), 3.80 (d, J = 6.2 Hz, 1H), 3.86 (d, J = 13.4 Hz, 1H), 4.01-4.08 (m, 2H), 4.58 (bd, 2H), 4.98 (bd, 3H), 5.20-5.67 (bs, 3 H), 7.65-7.72 (m, 2H), 8.03 (d, J = 1.76 Hz, 1H). IR (KBr)

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3400, 2930, 1550, 1300 and 1075 cm^{-1} ; mass spectrum [(-)FAB], m/z 526 ($M - H$);
Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{ClNO}_{12}\text{S} \cdot \text{H}_2\text{O}$: C, 41.80; H, 5.13; N, 2.56, Found: C, 41.35;
H, 4.89; N, 2.40.

5

Example 19

N-{2-Chloro-5-[β -D-maltosyl-1-thio)-methyl]-phenyl}-acetamide

The title compound was prepared as a white solid from *N*-{2-chloro-5-[hepta-
10 *O*-acetyl- β -D-maltosyl-1-thio)-methyl]-phenyl}-acetamide using a procedure similar
to step 2 of **Example 9**, mp 120-125 $^{\circ}\text{C}$; ^1H NMR ($\text{CD}_3\text{OD}-d_4$) δ 2.17 (s, 3H), 3.23-
3.33 (m, 3H), 3.41 (dd, $J = 9.9, 3.7$, Hz, 1H), 3.52-3.83 (m, 8H), 3.89 (dd, $J = 12.3,$
2.0, Hz, 1H), 4.00 (d, $J = 13.2$ Hz, 1H), 4.20 (d, $J = 9.9$ Hz, 1H), 5.15 (d, $J = 4.0$ Hz,
1H), 7.20 (dd, $J = 8.4, 1.8$, Hz, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 7.74 (s, 1H); IR (KBr)
15 3400, 2900, 1600, 1550 and 1050 cm^{-1} ; mass spectrum [(-)FAB], m/z 538 ($M - H$);
Anal. Calcd. for $\text{C}_{21}\text{H}_{30}\text{ClNO}_{11}\text{S} \cdot 1.0 \text{H}_2\text{O}$: C, 45.20; H, 5.78; N, 2.51, Found: C,
45.43; H, 5.62; N, 2.43.

20 Example 20

5-[[6,6'-Bis-*O*-(4-toluenesulfonyl)- β -maltosyl]-oxy-methyl]-2-methyl-1- nitrobenzene

step 1

5-[(β -Maltosyl)-oxy-methyl]-2-methyl-1-nitrobenzene

25 A stirred solution containing 5-[(hepta-*O*-acetyl- β -maltosyl)-oxy-methyl]-2-
methyl-1-nitrobenzene (prepared from 4-methyl-3-nitrobenzyl alcohol and
acetobromomaltose using procedures similar to **Example 1**)(0.835 g, 1.06 mmol)
and 25 weight% NaOMe/MeOH (0.115 g, 0.531 mmol) in MeOH (25 mL) was
refluxed for 4h. The reaction was cooled to ambient temperature and concentrated in
30 vacuo. Purification by reverse phase HPLC (C18, 25% $\text{CH}_3\text{CN}:\text{H}_2\text{O}$) gave 0.380 g
(73%) of the title compound as a white foam; ^1H NMR ($\text{DMSO}-d_6$) δ 2.50 (s, 3H),
3.60-3.21 (m, 2H), 3.22-3.57 (m, 7H), 3.59-3.65 (m, 2H), 3.71-3.73 (m, 2H), 4.31 (d,

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1H), 4.51-4.54 (m, 2H), 4.67 (d, 1H), 4.87-4.91 (m, 3H), 5.02 (d, 1H), 5.29 (d, 1H), 5.44 (d, 1H), 5.53 (d, 1H), 7.48 (d, 1H), 7.64 (dd, 1H), 8.01 (s, 1H).

step 2

5 **5-[[6,6'-Bis-*O*-(4-toluenesulfonyl)- β -maltosyl]-oxy-methyl]-2-methyl-1-nitrobenzene**

At 0 °C, to a stirred solution of 5-[(β -maltosyl)-oxy-methyl]-2-methyl-1-nitrobenzene (0.380 g, 0.774 mmol) in pyridine (4.5 mL) was added portionwise a solution of p-toluenesulfonyl chloride (0.812 g, 4.25 mmol) in CH₂Cl₂ (4.5 mL), over
10 a period of 5 h. The reaction was quenched with H₂O (30 mL) and extracted with EtOAc. The combined organic extracts were washed successively with sat. aq. NaHCO₃ (3x), with sat. aq. CuSO₄ (3x), with brine (3x), dried (Na₂SO₄) and concentrated. Purification by preparative HPLC (C18, 65% CH₃CN:H₂O) gave
15 0.373 g (59%) of the title compound as a white solid, mp 85-92 °C; ¹H NMR (DMSO-*d*₆) δ 2.34 (s, 3H), 2.40 (s, 3H), 2.48 (s, 3H), 3.01-3.10 (m, 2H), 3.12-3.17 (m, 1H), 3.23-3.40 (m, 3H), 3.51-3.55 (m, 2H), 4.02-4.14 (m, 3H), 4.23-4.29 (m, 2H), 4.63 (ABq, J = 13.1 Hz, $\Delta\delta$ = 0.05, 2H), 4.92 (d, 1H), 5.01 (d, 1H), 5.22 (d, 1H), 5.36 (d, 1H), 5.48 (d, 1H), 5.54 (d, 1H), 7.39 (d, 2H), 7.45-7.48 (m, 3H), 7.60 (dd, 1H), 7.71-7.77 (m, 4H), 7.96 (s, 1H); IR (KBr) 3380, 2920, 1600, 1530, 1360
20 and 1175 cm⁻¹; mass spectrum [(+) FAB], m/z 822 (M + Na)⁺; Anal. Calcd. for C₃₄H₄₁NO₁₇S₂ · H₂O: C, 49.93; H, 5.17; N, 1.75, Found: C, 49.77; H, 4.94; N, 1.70.

Example 21

25 **5-[[2,2',3,3',4'-Penta-*O*-acetyl-6,6'-bis-*O*-(4-toluenesulfonyl)- β -maltosyl]-oxy-methyl]-2-methyl-1-nitrobenzene**

At 0 °C, to a stirred solution containing 5-[[6,6'-bis-*O*-(4-toluenesulfonyl)- β -maltosyl]-oxy-methyl]-2-methyl-1-nitrobenzene (1.79 g, 2.24 mmol), pyridine (5.43 mL, 67.1 mmol) and 4-dimethylaminopyridine (1.25 g, 11.2 mmol) was added
30 dropwise acetic anhydride (2.09 mL, 22.4 mmol). After 3 h, the reaction eventually warmed to room temperature. The solution was diluted with diethyl ether (100 mL), washed successively with H₂O (2x), sat. aq. NaHCO₃ (2x), sat. aq. CuSO₄ (2x), brine

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(2x), dried (Na_2SO_4) and concentrated. Purification by flash chromatography (3, 4 and 5% $\text{MeOH}:\text{CHCl}_3$ gradient) gave 1.785 g, (79%), of the title compound as a white solid after crystallization from $\text{EtOAc}:\text{hexane}$, mp $83\text{ }^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$) δ 1.910 (s, 3H), 1.918 (s, 3H), 1.920 (s, 3H), 1.924 (s, 3H), 1.932 (s, 3H), 2.36 (s, 3H), 2.42 (s, 3H), 2.51 (s, 3H), 3.66 (t, 1H), 3.86 (dd, 1H), 3.92-3.96 (m, 1H), 4.06 (dd, 1H), 4.16-4.29 (m, 3H), 4.51-4.60 (m, 2H), 4.64-4.72 (m, 2H), 4.79 (d, 1H), 4.89 (t, 1H), 5.06-5.13 (m, 2H), 5.24 (t, 1H), 7.43 (d, 2H), 7.47-7.50 (m, 4H), 7.74-7.77 (m, 4H), 7.84 (s, 1H); mass spectrum [(+) FAB], m/z 1010 ($\text{M} + \text{H}$) $^+$; Anal. Calcd. for $\text{C}_{44}\text{H}_{51}\text{NO}_{22}\text{S}_2$: C, 52.32; H, 5.09; N, 1.39, Found: C, 52.46; H, 5.15; N, 1.41.

Example 22

5-[[6,6'-Dideoxy-6,6'-bis(4-nitro-imidazol-1-yl)- β -maltosyl]-oxy-methyl]-2-methyl-1-nitrobenzene

At ambient temperature, to a stirred solution of 4-nitroimidazole (0.478 g, 4.23 mmol) in DMF (8 mL) was added K_2CO_3 (0.278 g, 2.01 mmol). After 0.5h, to the reaction was added a solution of 5-[[6,6'-bis-O-(4-toluenesulfonyl)- β -maltosyl]-oxy-methyl]-2-methyl-1-nitrobenzene (1.61 g, 0.201 mmol) in DMF (20 mL) and the reaction was heated at $100\text{ }^\circ\text{C}$ for 24h. The reaction was concentrated in vacuo. Purification by reverse phase HPLC (C18, 30% $\text{CH}_3\text{CN}:\text{H}_2\text{O}$) gave 0.40 g (29%) of the title compound as a white solid, mp $146\text{ }^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$) δ 2.48 (s, 3H), 2.89 (t, 1H), 3.08 (t, 1H), 3.20-3.29 (m, 2H), 3.40-3.47 (m, 2H), 3.64 (dt, 1H), 3.88 (dd, 1H), 3.97-4.03 (m, 2H), 4.21-4.27 (m, 2H), 4.43-4.47 (m, 2H), 4.59 (d, 1H), 5.11 (d, 1H), 5.17 (d, 1H), 5.40 (br. s, 1H), 5.57 (br. s, 1H), 5.68 (br. s, 1H), 5.84 (br. s, 1H), 7.41-7.46 (m, 2H), 7.65 (d, 1H), 7.74 (d, 1H), 7.85 (s, 1H), 8.22 (d, 1H), 8.25 (d, 1H); mass spectrum [(+) FAB], m/z 682 ($\text{M} + \text{H}$) $^+$; Anal. Calcd. for $\text{C}_{26}\text{H}_{31}\text{N}_7\text{O}_{15} \cdot 2\text{H}_2\text{O}$: C, 43.52; H, 4.92; N, 13.66, Found: C, 43.90; H, 4.72; N, 13.31.

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Example 23

5-{[2,2',3,3',4'-Penta-O-acetyl-6,6'-dideoxy-6,6'-bis(4-nitro-imidazol-1-yl)- β -maltosyl]-oxy-methyl}-2-methyl-1-nitrobenzene

At ambient temperature, to a stirred solution of 4-nitroimidazole (0.177 g, 1.57 mmol) in DMF (3 mL) was added K_2CO_3 (0.103 g, 0.747 mmol). After 0.5h, to the reaction was added a solution of 5-{[2,2',3,3',4'-penta-O-acetyl-6,6'-bis-O-(4-toluenesulfonyl)- β -maltosyl]-oxy-methyl}-2-methyl-1-nitrobenzene (0.754 g, 0.747 mmol) in DMF (7 mL) and the reaction was heated at 100 °C for 4h. At ambient temperature, the reaction was quenched with ice cold H_2O (50 mL) and extracted with EtOAc. The organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography (5, 6 and 7% MeOH: $CHCl_3$ gradient) gave 0.315 g, (47%), of the title compound as a white solid after crystallization from EtOAc:hexane, mp 140 °C; 1H NMR ($DMSO-d_6$) δ 1.92 (s, 3H), 1.93 (s, 3H), 1.94 (s, 6H), 2.08 (s, 3H), 2.49 (s, 3H), 3.64 (dd, 1H), 3.91 (t, 1H), 4.00-4.06 (m, 1H), 4.27-4.40 (m, 5H), 4.54 (d, 1H), 4.74-4.79 (m, 3H), 4.96 (dd, 1H), 5.22-5.30 (m, 3H), 7.33 (dd, 1H), 7.43 (d, 1H), 7.69 (d, 1H), 7.72 (d, 1H), 7.77 (d, 1H), 8.26 (d, 1H), 8.34 (d, 1H); mass spectrum [(+) FAB], m/z 892 ($M + H$) $^+$; Anal. Calcd. for $C_{36}H_{41}N_7O_{20}$: C, 48.49; H, 4.63; N, 11.00, Found: C, 48.32; H, 4.52; N, 10.90.